UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,061	02/27/2007	Michel Cogne	1169-044	1063

20529 7590 08/02/2010

THE NATH LAW GROUP
112 South West Street
Alexandria, VA 22314

EXAMINER	
LI, QIAN JANICE	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
08/02/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,061	COGNE ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-73* is/are pending in the application.

4a) Of the above claim(s) *60-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and remarks filed 5/5/2010 are acknowledged. Claims 32, 38-40, 42, 43, 46-50, 52, 53, 56-58 have been amended.

Claims 36-73 are pending, Claims 60-73 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions. Claims 36-59 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims or persuasive arguments and new grounds of rejections will not be reiterated. The arguments in 5/5/10 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 36-57, 59 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Green et al*. (USP 7,547,817) in view of *Luby et al*. (J Exp Med 2001;193:159-68).

Green teaches making a transgenic mouse for producing specific isotypes of human antibodies, wherein the transgenic mouse whose endogenous immunoglobulin gene was partially replaced with a human immunoglobulin heavy chain transgene including constant and variable regions and the exon encoding the CH3 domain and a membrane exon, a non-cognate switch region (e.g. the abstract and column 12) relative to the C_H gene (= deleting mouse Sμ, replacing it with a heterologous one from corresponding constant region). For example, *Green* teaches:

> In another embodiment, the human C.gamma.2 coding sequences, including all of the exons for the secreted and membrane-bound forms of the C.sub.H gene are replaced by another human C.sub.H gene. In this way, the human S.gamma.2 sequences control CSR from C.sub..mu. to the downstream C.sub.H gene. It is known that the hSg2 sequences are stable in yH1C while other human S sequences, some of which have longer tandem arrays of S repeats may be less stable. It is also known that CSR in transgenic mice with the human C.gamma.2 gene is efficient and generates high serum levels of human IgG2 and results in efficient production of fully human IgG2 mAbs. Thus, it may be preferable to retain the human S.gamma.2 with their favorable stability and in vivo response to antigen challenge while engineering CSR to occur to another isotype, e.g., either C.gamma.1 or C.gamma.4. To accomplish this, a vector with the following elements would be constructed: 5' homology located between human S.gamma.2 and the human C.gamma.2 coding exon 1, a human CH gene other than C.gamma.2, the mouse 3' enhancer, a yeast selectable marker, and 3' targeting homology in the YAC arm for example. (Emphasis added)

Here, the recited C.sub.H gene apparently includes Cα IgH locus. For example, when discussing the role of enhancers, *Green* mentioned the importance of a cluster of enhancers 3' of the Cα gene (column 13).

The exemplified transgenic mouse comprising a gene encoding human Ig kappa light chain (see e.g. claims 1, 2 and figure 1). *Green* teaches using the transgenic mouse for producing a [any] desired specific isotypes of human antibodies, wherein the endogenous IgH loci were inactivated (e.g. claim 3).

Green also teaches a targeting vector (e.g. the cited text *supra*) and ES cells comprising the vector, wherein the vector comprises the human IgH transgene composed of 66 VH, all the D and J elements, Cμ, Cδ, all regulatory elements, and all in germline configuration (column 10), which would include the heavy chain promoter. The vector also comprises intronic Eμ upstream, and palindrome hs3a/hs1,2/hs3b downstream (column 13), loxP sites and flanking (mouse) sequences of 5'- and 3'-targeting homology for homologous recombination (e.g. column 15). *Green* also teaches introducing the targeting vector into mouse ES cells (e.g. example 27), and breeding to homozygosis (e.g. example 29).

Green differs from instant claimed in that the inserted C_H gene operably linked to a non-cognate switch sequence whereas a preferred embodiment of instantly claimed transgenic animal does not contain a switch sequence. However, it is noted instant claims embrace a transgene comprising a non-cognate switch sequence.

Luby supplemented *Green* by establishing at the time of instant priority date, it was well known in the art that μ switch tandem repeats (Sμ) is important but not

required for antibody class switch. *Luby* teaches a Sμ–deleted transgenic mouse made by homologous recombination, whose serum levels of antibodies showed slight reduction in IgG1 and IgG3, larger reduction in IgG2b, but no reduction in IgA (e.g. last paragraph, page 161). The switch region Sμ in the targeting vector disclosed by *Luby* was deleted and replaced with a loxP recombinase recognition site downstream of Eμ and upstream of Cμ, providing a universal insertion site for insertion of any transgene of interest including Cα gene (figure 1). *Luby* concluded that sequences outside of the Sμ must be capable of directing class switch, while the absence of the Sμ may affect the efficiency of IgG production, but not the efficiency of IgA production.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the mouse taught by *Green* by replacing the mouse Sμ region with any constant region of interest using the construct as taught by either *Green* or *Luby* and particularly when the intended antibody to make is a human IgA and when the C_H is Cα as taught by *Green* in view of *Luby* to arrive at instantly claimed invention. Given the levels of the skilled as illustrated by *Green* in view of *Luby*, one would have had a reasonable expectation of success.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant listed seven features which allegedly were not taught by *Green*. The arguments would be addressed as following in the order they appeared.

1. The applicant argues that Green does not disclose a knock-in mammal generate by homologous recombination at the mammal endogenous IgH locus but the Xenomouse™ was generated by random insertion of a large human IgH locus using YAC vectors.

The argument has been fully considered but found not persuasive. As an initial matter, claims 36-52 do not require homologous recombination, as long as a non-human mammal comprising a modified endogenous IgH locus and deletion of endogenous Sμ and a human class A Ig Cα gene.

More importantly, none of the cited text in the remarks supporting the applicant's assertion that the xenomouse was produced via random insertion of large genomic segment. To the contrary, *Green* clearly states in the context of making the xenomouse "More particularly, there have been deletions of key elements of the mouse IgH and Igk loci by homologous recombination in mouse embryonic stem cells, followed by germline transmission of the mutations and subsequent breeding to produce mice which are homozygous for both inactivated loci (DI mice)" (paragraph bridging columns 9-10).

As to the YAC vector, *Green* repeatedly teaches constructing the yeast carrier with homologous human and mouse sequences. For example, *Green* states, "Yeast artificial chromosomes as cloning vectors in combination with gene targeting of endogenous loci and breeding of transgenic strains provided one solution to the problem of antibody diversity" (col 2, line 55-58). Figures 5-7 are schematic diagram for YAC targeting vectors, wherein a 5' homology sequence located between switch sequence and human C_H gene, a selection marker, 3' enhancer and 3' targeting mouse homology were present in the YAC arm. (e.g. column 13, lines 2-7 and also see column 10, lines 24-27). As such, it would have been clear to the skilled in the art to make the claimed mouse with homologous recombination.

2. The applicant argues Green dose not disclose targeted DNA sequence replacement at the mouse endogenous IgH locus.

The argument has been addressed *supra*.

3. The applicant argues Green does not disclose targeted DNA sequence replacement, wherein the endogenous switch sequence $S\mu$ is replaced with a transgene construct comprising a human heavy chain $C\alpha$ region but rather *Green* teaches a construct comprising either mouse or human switch region.

In response, the rejected claims do not require the absence of a switch region as long as the transgene recipient's switch region is replaced; and the claims are inclusive that a non-cognate switch region may be present.

Newly cited reference by *Luby* clearly illustrated that it was known in the art deletion of the Sμ region would not reduce the efficiency of class switch for the production of IgA. Accordingly, the claimed invention as a whole was *prima facie* obvious.

4. The applicant argues Green does not disclose the insertion of a human CH transgene which is not linked to a switch region.

In response, the rejected claims are in the format of an open language, and do not require the absence of a switch region as long as the transgene recipient's switch region is replaced; the claims are inclusive that a non-cognate switch region may be present. Newly cited reference by *Luby* clearly illustrated that it was known in the art deletion of the Sμ region would not reduce the efficiency of class switch for the production of IgA. Hence, if the inserted C_H was Cα, the skilled in the art would have the knowledge and option of either including or deleting the Sμ.

5. The applicant argues Green does not disclose the insertion of a human CH transgene between the intronic enhancer Eμ and Cμ gene but downstream of the Cm gene.

In response, none of the claims require the insertion of a human C_H between the intronic enhancer Eμ and Cμ gene, claims 43 and 52 mentioned the intronic enhancer Eμ and the palindrome hs3a/hs1,2/hs3b (=m3'E of *Green*) are positioned around a human Ig light chain gene. The figures in Green do not include the position of Cμ.

Moreover, the targeting vector as disclosed by *Luby* clearly provides the option of positioning Cα in between of intronic enhancer Eμ and Cμ gene (see figure 1).

6. The applicant argues Green does not disclose a modified IgH locus that is incapable of isotype switching from IgM to the isotype of the downstream human CH transgene.

In response, these limitations are not in the rejected claims.

7. The applicant argues Green does not disclose a transgeneic mammal which produces no IgM and high level of chimeric human IgAs.

Again these limitations are not in the rejected claims, but would have been obvious over *Green* in view of *Luby*.

In response to applicant's argument that the references fail to show certain features of applicant's invention as listed above (e.g. 5, 6, 7), it is noted that the features upon which applicant relies are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The applicant went on to argue *Qiu* discloses an Iα knock-out mouse, the endogenous switch region and Cα region are not modified and there is no human Sα and Cα insertion.

The argument is now moot.

The applicant then argues that the prior art and the common knowledge at the time of filing teach away from the present invention referring to Annex I. The applicant asserts it was known in the art that B cell maturation *in vivo* requires the development of IgM producing B cells which subsequently undergo isotype class switch from IgM to the

IgG or IgA. …"to produce human Ig of the desired isotype (IgG, IgA) one of ordinary skill in the art would never have engineered mice which do not produce IgM but only Ig of another isotype".

In response, claims are given the broadest reasonable interpretation, as such, none of the claims require engineered mice which do not produce IgM but only Ig of another isotype, the claims only require replacing an endogenous switch region Sμ with a transgene comprising a human class A Ig Cα, at least an exon encoding the CH3 domain and a membrane exon, which does not exclude the presence of an exogenous switch region and other human Ig genes.

Moreover, it is noted *Green* reported the Cγ transgenic mouse produced significant baseline levels of human IgG in the absence of immunization, i.e. without going through the class switch process (e.g. see example 10), it only takes efficient expression of the transgene, which was routine in the art. Hence, for producing a desired type of isotype antibodies, one could just insert only the desired human Ig gene while inactivate endogenous one, such could be achieved without class switch.

Accordingly, the rejection stands.

Claim 58 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Green et al*. (USP 7,547,817) in view of in view of *Luby et al*. (J Exp Med 2001;193:159-68) as applied to claims 36-57, 59 above, further in view of GeneBank AC073553 (September 2002), for reasons *supra* and following.

The teaching of *Green* in view of *Luby* does not specifically mention the sequences as indicated as SEQ ID Nos: 7 & 8.

However, the sequences were available in the art at the time of the priority date. Accordingly, it would have been obvious for the skilled intending to make a human IgH Cα transgenic mouse to use the available sequences as flanking sequence of the targeting vector. Given the knowledge of the skilled in the art, the claimed invention was *prima facie* obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-51, 59 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The claims embrace any transgenic non-human mammal (beyond mouse) having a modified IgH locus. The specification discloses a transgenic mouse comprising a human IgH locus by replacing a mouse switch sequence with a human Cα gene made by homologous recombination using mouse embryonic stem (ES) cells, which require the knowledge of sequences of IgH locus for the genus of non-human mammal, which were not known in the prior art nor taught by the specification.

An adequate written description for a genus of IgH locus requires more than a mere statement that it is part of the invention; what is required is a description of the sequences themselves. With respect to method claims, adequate description of the methods first requires an adequate description of the materials, i.e. a genus of IgH, which provides the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the genus of IgH locus. Therefore, only the described mouse IgH meets the written description provision of 35 U.S.C. §112, first paragraph.

Response to Arguments

Applicant argues only a very small portion of sequences flanking the Sμ region are necessary for practice the claimed invention and these sequences are available for several animal species.

Applicant's arguments have been fully considered but they are not persuasive.

The written description requirement measures possession at the time of the priority date. To this end, the applicant fails to establish they were in possession of the genus of the claimed non-human transgenic *animals*.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 36-51, 59 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for providing a transgenic mouse comprising a modified IgH locus as claimed, does not reasonably provide enablement for a genus non-human transgenic mammals comprising a modified IgH locus as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction

provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

To the extent that the essential materials used in the claimed method are not adequately described by the instant disclosure, claims 36-51, 59 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described, which is not conventional in the art.

The claims embrace any transgenic non-human mammal (beyond mouse) having a modified IgH locus. The specification discloses a transgenic mouse comprising a human IgH locus by replacing a mouse switch sequence with a human Cα gene made by homologous recombination using mouse embryonic stem (ES) cells. With respect to ES cells, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and only "putative" ES (ES-like) cells exist for other species (see *Moreadith et al.*, **J. Mol. Med.** 1997;75(3):208-16, e.g. S*ummary*). Note that "putative" ES cells lack a demonstration of giving rise to germline tissue (germline transmission) or the whole animal (totipotency), a demonstration which is an art-recognized property of ES cells. Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of any non-human mammal ES cells, other than the mouse. Without germline transmission, breeding to homozygosity would be impossible. Accordingly, the claims appear to be only enabled for mouse. *Mullin et al*. supports this observation as they discuss the generation of non-mouse transgenics, *Mullins et al*. (**Journal of Clinical Investigation**, 1996) report that "ALTHOUGH TO DATE CHIMERIC ANIMALS HAVE BEEN GENERATED FROM SEVERAL SPECIES INCLUDING THE PIG, IN NO SPECIES OTHER THAN THE MOUSE HAS GERMLINE TRANSMISSION OF AN ES CELL BEEN SUCCESSFULLY DEMONSTRATED. THIS REMAIN A MAJOR GOAL FOR THE FUTURE AND MAY WELL REQUIRE THE USE OF NOVEL STRATEGIES WHICH DEPART WIDELY FROM THE TRADITIONAL METHODS USED IN THE MOUSE" (page 1558, column 2, first paragraph). Moreover, although the specification teaches methods to generate transgenic mice whose genome comprising a human IgH Cα gene, the specification fails to teach methods of generating any other transgenic animals. It was known in the art, just murine subgenus of animal genus encompasses more than 1383 species of rodents, and one of skill would not be able to rely on the state of the transgenic art for an attempt to produce transgenic animals for the breadth claimed.

Without homologous recombination in ES cells, the animal has to be made through microinjection of fertilized eggs, and somatic cell nuclear transfer. It was highly unpredictable whether one could make the genus of modified IgH animals, wherein the animal producing human IgA antibodies. This is because the aforementioned techniques were still under-development, and highly unpredictable.

The process of pronuclear microinjection is highly inefficient at the time of the filing. This is because the art of transgenic animals has for many years stated that the

unpredictability lies with the site or sites of integration of the transgene into the target genome, which would vary among different species of animals. The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994 J. Biotech. 34, page 281). Moreover, *Mullins* (**J Clin Invest**, 1996;97:1557-60) teaches, the major problems regarding pronuclear microinjection is that the exogenous DNA integrates randomly into chromosomal DNA, and that mouse-derived agents do not adequately prevent differentiation of stem cells in species other than mouse (left column, page 1558). *Mullins* concludes that "THE USE OF NONMURINE SPECIES FOR TRANSGENESIS WILL CONTINUE TO REFLECT THE SUITABILITY OF A PARTICULAR SPECIES FOR THE SPECIFIC QUESTIONS BEING ADDRESSED, BEARING IN MIND THAT A GIVEN CONSTRUCT MAY REACT VERY DIFFERENTLY FROM ONE SPECIES TO ANOTHER." (page S39, Summary). *Wall* (J Dairy Sci 1997;80:2213-24) states that "TRANSGENE EXPRESSION AND THE PHYSIOLOGICAL CONSEQUENCES OF TRANSGENE PRODUCTS IN LIVESTOCK ARE NOT ALWAYS PREDICTED IN TRANSGENIC MOUSE STUDIES" (page 2215, first paragraph).

The same is true for somatic cells nuclear cell transfer cloning. For example, *Denning* (Nat Biotech 2001;19:559-562) teaches difficulties of somatic cell cloning, "A SUBSTANTIAL NUMBER OF COLONIES WITH ONLY TARGETED CELLS SENESCED BEFORE THEY COULD BE PREPARED FOR NUCLEAR TRANSFER. THE HIGH ATTRITION RATE OF TARGETED CLONAL POPULATIONS SUITABLE FOR NUCLEAR TRANSFER REPRESENTS ONE OF THE MAJOR HURDLES OF GENE TARGETING IN PRIMARY SOMATIC CELLS" (left column, page 560). The unpredictability also lies with the faulty epigenetic reprogramming in nuclei cloning. Since the applicants have not disclosed other animal species encompassed by the claims, it is highly unpredictable of the outcome of the recited method in making any animal. *Yanagimachi* (Mol Cell Endocrinol 2002;187:241-8) teaches, at a post-filing date, that "CLONING EFFICIENCY-AS DETERMINED BY THE PROPORTION OF LIVE OFFSPRING DEVELOPED FROM ALL OOCYTES THAT RECEIVED DONOR CELL NUCLEI-IS LOW REGARDLESS OF THE CELL TYPE (INCLUDING, EMBRYONIC STEM CELLS) AND ANIMAL SPECIES USED. IN ALL ANIMALS EXCEPT OF JAPANESE BLACK BEEF CATTLE, THE VAST MAJORITY OF CLONED EMBRYOS PERISH BEFORE REACHING FULL TERM" (Abstract), and "THUS FAR, CLONED OFFSPRING THAT SURVIVED BIRTH AND REACHED ADULTHOOD WERE THE EXCEPTION RATHER THAN THE RULE (page 243, left column, emphasis added). *Yanagimachi* goes on to teach, "THIS LOW EFFICIENCY OF CLONING SEEMS TO BE DUE LARGELY TO FAULTY EPIGENETIC REPROGRAMMING OF DONOR CELL NUCLEI AFTER TRANSFER INTO RECIPIENT OOCYTES. CLONED EMBRYOS WITH MAJOR EPIGENETIC ERRORS DIE BEFORE OR SOON AFTER IMPLANTATION" (abstract). *Wilmut* (Cloning Stem Cell 2003;5:99-100) teaches, "BY THE TIME OF DOLLY'S DEATH IN 2003, CLONES HAD BEEN DERIVED FROM ADULT CELLS OF SEVERN MAMMALIAN SPECIES, BUT THE SAME TECHNIQUES WERE NOT SUCCESSFUL IN SEVEN OTHERS, DESPITE INTENSIVE EFFORTS BY EXPERIENCED RESEARCH TEAMS. THESE INCLUDE RHESUS MONKEY, RAT, DOG, AND HORSE. THIS FAILURE EMPHASIZES THE IMPORTANCE OF DIFFERENTCES BETWEEN SPECIES. THE DIFFERENCE MIGHT BE IN THE MOLECULAR MECHANISMS THAT REGULATE EARLY DEVELOPMENT OR IN ENABLING TECHNIQUES FOR OOCYTE RECOVERY, EMBRYO CULTURE, OR EMBRYO TRANSFER. SUCH DIFFERENCES HAVE ALREADY BEEN IDENTIFIED BETWEEN THE SPECIES FROM WHICH CLONES HAVE BEEN DERIVED", and "THE MOST STRIKING THING ABOUT THE TECHNIQUES THAT EMERGED DURING DOLLY'S LIFE IS THAT MAMMALIAN CLONING REMAINS A

REPEATABLE, BUT INEFFICIENT PROCEDURE…AN EXTRAORDINARY VARIETY OF ABNORMALITIES HAVE BEEN DESCRIBED IN CLONED EMBRYOS, FETURESES, AND OFFSPRING".

Polejaeva et al (Nature 2000;407:86) teach, "TO DATE, THE EFFICIENCY OF SOMATIC CELL NUCLEAR TRANSFER, WHEN MEASURED AS DEVELOPMENT TO TERM AS A PROPORTION OF OOCYTES USED, HAS BEEN VERY LOW (1-2%). A VARIETY OF FACTORS PROBABLY CONTRIBUTE TO THIS INEFFICIENCY THESES INCLUDE LABORATORY TO LABORATORY VARIATION, OOCYTE SOURCE AND QUALITY, METHODS OF EMBRYO CULTURE, DONOR CELL TYPE, POSSIBLE LOSS OF SOMATIC IMPRINTING IN THE NUCLEI OF THE RECONSTRUCTED EMBRYO, FAILURE TO REPROGRAM THE TRANSPLANTED NUCLEUS ADEQUATELY, AND FINALLY, THE FAILURE OF ARTIFICIAL METHODS OF ACTIVATION TO EMULATE REPRODUCIBLY THOSE CRUCIAL MEMBRANE-MEDIATED EVENTS THAT ACCOMPANY FERTILIZATION" (1st paragraph). Apparently, it was not, and has yet to become routine in the art to obtain a nonhuman transgenic livestock such as a transgenic pig having human Cα and producing human IgA. The skilled in the art intending to practice the claimed invention would have to carry out undue experimentation to make the claimed non-human transgenic mammals while the efficiency of the process would be expected low (<=1%) and phenotypic outcome of the mammal is unpredictable due to the many variant factors as discussed *supra*.

Accordingly, in view of the state of the art and the quantity of experimentation necessary for making any human IgH Cα transgenic non-human mammal producing a human IgA, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to any transgenic non-human animal whose genome comprises a homologous disruption of endogenous *IgH* gene and a transgenic human IgH Cα, and the breadth of the claims, other than the exemplified mouse, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Response to Arguments

The applicant argues the essential materials (IgH sequences) required for practicing the claimed invention are adequately described by the instant disclosure and the specification describes how the claimed transgenic mammal can be obtained by homologous recombination with an targeting vector.

The argument has been fully considered but found not persuasive for reasons of record and following.

As indicated previously, the applicant fails to provide the essential material for homologous recombination in a species beyond mouse, i.e. ES cells for species beyond mouse.

The applicant then argues that the inefficiency of pronuclear microinjection is not a relevant problem since the transgene is integrated by homologous recombination in a functional locus. Applicant cited *Mullin*, asserting that targeted homologous recombination improved the inefficiency of pronuclear microinjection.

In response, overcoming position effect by including large amounts of flanking sequences in a random insertion vector was not homologous recombination, it's an effort to overcome the unwanted effect of random insertion. Moreover, long after *Mullin* publication, *Wall* (Cloning Stem Cells 2001;3:209-220) reviewed the efforts in the art for realizing homologous recombination via pronuclear injection, and reported it was highly inefficient for the HR event to occur and for such event to be detected (see e.g. page 214). *Wall* states,

> Undaunted by the seemingly impossible odds,
> some researchers have recently included sequences
> in their transgene constructs homologous
> with repetitive sequences in the genome.
> Though some claimed increased integration rates
> in embryos (Kang et al., 2000), the results remain
> to be confirmed with live-born transgenic animals.
> For others, as might be expected, it appears
> that their efforts were in vain (Pintado and
> Gutierrez-Adan, 2001; Rieth et al., 1999).

To this end, the specification fails to shed new lights on how to improve the extreme inefficiency, and fails to provide an enabling disclosure for what is now broadly

claimed, it would have required undue experimentation for the skilled intending to practice the broadly claimed invention.

Accordingly, for reasons of record and *supra*, the rejection stands.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9 AM -7:00pm, Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI/
Primary Examiner, Art Unit 1633